

JC19 Rec'd PCT/PTO 21 MAY 2001

PTO 1390 Page 1 of 1

U.S. Dept. of Commerce Pat. & Trademark Office

Attorney's Docket No.

21838

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 USC 371

US. Application No. (if known)

09/856517

INTERNATIONAL APP. NO.
PCT/HU99/00102

INTERNATIONAL FILING DATE
23 December 1999

PRIORITY DATE CLAIMED
29 December 1998

TITLE OF INVENTION

PROCESS FOR THE SYNTHESIS OF 1-(AMINOMETHYL)CYCLOHEXYL-ACETIC ACID

APPLICANT(S) FOR DO/EO/US

Tibor GIZUR et al

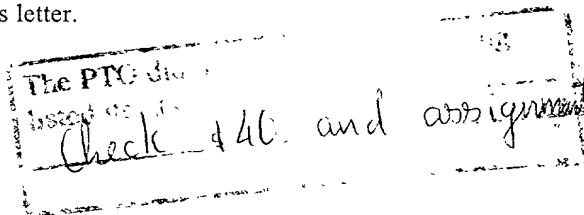
Applicant herewith submits to the United States Designated/Elected Office (DO/EU/US) the following .

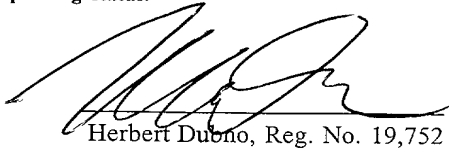
1. ☒ This is a **FIRST** submission of items concerning a filing under 35 USC 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 USC 371.
3. ☐ This is an express request to begin national examination procedures (35 USC 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 USC 317(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 USC 371(c)(2)). (IN ENGLISH)
 - a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau.
 - b. ☐ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Patent Office.
6. ☐ A translation of the International application into English.
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 USC 371(c)(3)).
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau.
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however the time limit for making such amendments has NOT expired.
 - d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 USC 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 USC 371(c)(4)).
10. ☒ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 USC 371(c)(5)).

Items 11. to 16. below concern documents or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An Assignment for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.
☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items of information.

References
PTO-1449



US Application no. (if known) 09/856517		International Application no. PCT/HU99/00102	Attorney's Docket No. 21838
The following fees are submitted: Basic National Fee (37 CFR 1.492(a)(1)-(5): Search report has been prepared by the EPO or JP \$860.00 Int'l prel. exam. fee paid to USPTO (37 CFR 1.482) \$690.00 No int'l prel. exam. fee paid to USPTO (37 CFR 1.482) but int'l search fee paid to USPTO (37 CFR 1.445(a)(2)) \$710.00 Neither int'l prel. exam fee (37 CFR 1.482) nor int'l search fee (37 CFR 1.455(a)(2)) paid to USPTO \$1000.00 Intl. prel. exam. fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Art. 33(2-4) \$100.00 ENTER APPROPRIATE BASIC FEE AMOUNT Surcharge of \$130.00 for furnishing oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).			CALCULATIONS PTO USE ONLY rec'd PCT/PTO 21 MAY 2001 \$1,000
CLAIMS	NO. FILED	NO. EXTRA	RATE
Total claims	9	0	\$18
Ind. claims	5	2	\$80
MULTIPLE DEP. CLAIM(S) (if applicable) (see prel. amt.)			270
TOTAL OF ABOVE CALCULATIONS			\$1,160
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (37 CFR 1.2, 1.27, 1.28)			\$0
SUBTOTAL			\$1,160
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).			
TOTAL NATIONAL FEE			\$1,160
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The Assignment may be accompanied by an appropriate PTO-1595 cover sheet (37 CFR 3.28, 3.39)			\$40
TOTAL FEES ENCLOSED			\$1,200
			Amt to be refunded
			Amt to be charged
a. <input checked="" type="checkbox"/> A check in the amount of \$1160 to cover the above fees is enclosed b. <input checked="" type="checkbox"/> A check in the amount of \$40 to cover recordal of the Assignment c. <input type="checkbox"/> Please charge my deposit account 18-2025 \$00.00 to cover the above fees. A copy of this sheet is enclosed. d. <input type="checkbox"/> Please charge the amount due to the credit card identified in the attached PTO-2-38. e. <input checked="" type="checkbox"/> The commissioner is authorized to charge any additional fees which may be required or credit any overpayment to deposit account 18-2025. A copy of this sheet is enclosed			
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.			
Send all correspondence to: The Firm of Karl F. Ross P.C. 5676 Riverdale Ave. Box 900 Riverdale (Bronx), NY 10471			
			 Herbert Dubno, Reg. No. 19,752



09/856517
JC18 Rec'd PCT/PTO 21 MAY 2001

21838

IN THE U.S. PATENT AND TRADEMARK OFFICE

Inventor Tibor GIZUR et al
Patent App. Not known (US Nat'l phase of PCT/HU99/00102)
Filed Concurrently herewith
For PROCESS FOR THE SYNTHESIS OF 1-
(AMINOMETHYL)CYCLOHEXYL-ACETIC ACID
Art Unit Not known
Hon. Commissioner of Patents
Washington, DC 20231

PRELIMINARY AMENDMENT

Prior to examination of the above-identified application,
please amend as follows:

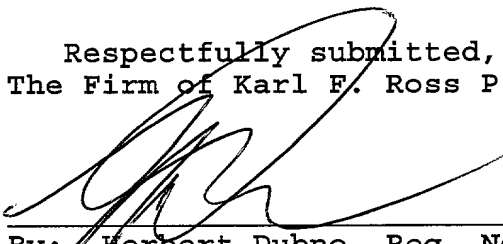
In the Claims:

Claim 4, line 1, delete "1-3", insert instead -- 1 --.

Claim 5, line 1, delete "1-3", insert instead -- 1 --.

This preliminary amendment is submitted just to reduce
claim charges.

Respectfully submitted,
The Firm of Karl F. Ross P.C.


By: Herbert Dubno, Reg. No. 19,752
Attorney for Applicant

18 May 2001
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rg

Process for the synthesis of 1-(aminomethyl)cyclohexyl-acetic acid

The invention relates to a new process for the synthesis of 1-(aminomethyl)cyclohexyl-acetic acid of the formula (I) via the new
5 intermediate 1-(nitromethyl)cyclohexyl-acetic acid derivative of general formula (II), wherein R represents hydrogen, benzyl group, diphenylmethyl group or C₁-C₄ alkyl or alkoxy aromatic ring substituted derivatives thereof.



(I)



(II)

The 1-(aminomethyl)cyclohexyl-acetic acid of formula (I), otherwise known as gabapentin is the active ingredient of the GABA antagonist drug. Several methods are known from the literature for the synthesis of
15 this compound.

In most of the known methods an intermediate is hydrolysed with acid, and gabapentin is obtained from the so formed gabapentin hydrochloride salt by using ion exchange resin. This process is described in the German patent No. DE 2 460 891, in which the 1,1-cyclohexyldiacetic acid anhydride is converted into hydroxamic acid and
20 the latter is transformed via Lossen degradation into the hydrochloride salt of the product. The US patent No. US 4 024 175 describes a method where the same 1,1-cyclohexyldiacetic acid anhydride is used as starting material. The anhydride is first transformed into a monomethyl ester monosalt and then a monoacid monoazide is obtained from it. The
25 gabapentin hydrochloride is prepared from the latter via Curtius degradation.

Similarly gabapentin hydrochloride is formed in the procedure described in the European patent No. EP 414 274. According to this

invention the alkyl ester of 1-(nitromethyl)acetic acid is transformed into a 2-aza-spiro[4,5]decane-3-on derivative by catalytic hydrogenation. The gabapentin hydrochloride is obtained from the latter lactam derivative by refluxing it with hydrochloric acid and gabapentin is isolated by using ion-exchange resin.

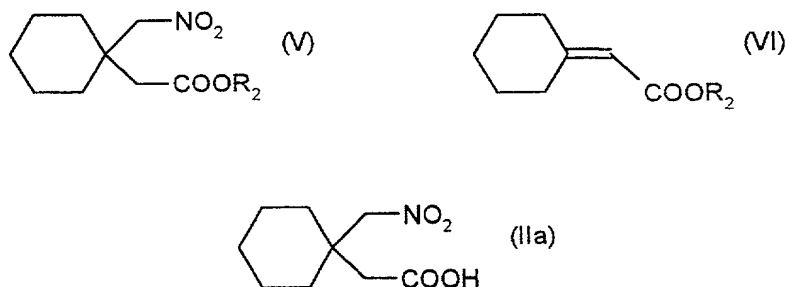
The disadvantages of the above mentioned procedures are as follows. The gabapentin is obtained as its hydrochloride salt and gabapentin itself can be isolated only by using labour-demanding and expensive ion-exchange method. To avoid the unwanted lactam formation side-reaction requires also a labour-demanding and expensive technique. Further disadvantages of these procedures are the use of hazardous reagents, e.g. potassium cyanide, sodium azide and the expensive pressure resistant equipment.

The procedure described in the European patent No. EP 414 275 avoids the formation of the lactam compound and the gabapentin hydrochloride, and this way the use of the expensive ion-exchange method. According to this procedure cyano-cyclohexane-maleinic acid derivatives are hydrolysed with base, decarboxylated and finally the nitril group is catalytically hydrogenated. On the other hand this patent does not describe the synthesis of the cyano-cyclohexane-maleinic acid derivatives, which is a multi step, tedious process. It is important to note, that the synthesis of the maleinic acid ester is four steps starting from cyclohexanon, so the synthesis of gabapentin is altogether seven steps. The patent does not mention the purity of the obtained gabapentin either, in contrast to other patents, which describe the synthesis of gabapentin, e.g. EP 414 274.

The aim the invention is to elaborate an economical, industrially applicable process for the synthesis of gabapentin, which eliminates the disadvantages of the above mentioned procedures and makes possible the simple synthesis of the very pure final product of formula (I) in fewer steps and in good yield.

The synthesis of gabapentin according to the process of the invention is as follows

- a) the alkyl ester of cyclohexylidene-acetic acid of general formula (VI) — wherein R_2 represents C_1 - C_4 alkyl group — is transformed into the alkyl ester of 1-(nitromethyl)cyclohexyl-acetic acid of general formula (V) —
 5 wherein the meaning of R_2 is as defined above — with nitromethane in the presence of a base, the latter is hydrolysed with aqueous methanolic solution of potassium hydroxide and the obtained 1-(nitromethyl)cyclohexyl-acetic acid of formula (IIa) is hydrogenated in a
 10 solvent in the presence of a catalyst to yield the desired product of formula (I), or



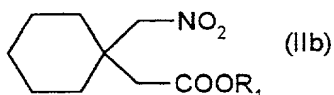
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- b) the alkyl ester of cyclohexylidene-acetic acid of general formula (VI) — wherein the meaning of R_2 is as defined above — is hydrolysed with aqueous methanolic solution of potassium hydroxide and the obtained cyclohexylidene-acetic acid of formula (IV) is reacted with a reagent of
 20 formula R_1 -X — wherein R_1 represents benzyl group, diphenylmethyl group or in given case C_1 - C_4 alkyl or alkoxy aromatic ring substituted derivatives thereof — to give the appropriate cyclohexylidene acid derivative of general formula (III) — wherein the meaning of R_1 is as
 25 defined above — and this intermediar is transformed into 1-(nitromethyl)cyclohexyl-acetic acid derivative of general formula (IIb) —

wherein the meaning of R_1 is as defined above — with nitromethane and the latter is hydrogenated in a solvent in the presence of a catalyst.



5



The process of the invention is illustrated on Scheme 1.

The invention based on the observation, that the reduction of the new compounds of general formula (II) at atmospheric pressure yields directly the pure desired final product.

Surprisingly it was found, that using the compounds of general formula (II) as starting materials in the reduction step the lactam compound is not formed, but the very pure gabapentin is obtained directly. This was not anticipated in the knowledge of previous procedures, as the ability of lactam formation of this type of compounds is known from the literature (e.g. EP 414 274).

The alkyl ester of cyclohexylideneacetic acid of general formula (VI) used as starting material can be prepared according to the literature via the reaction of cyclohexanone and the appropriate ester of diethylphosphono-acetic acid.

In the last hydrogenation step any catalysts can be used, which are generally applicable in hydrogenation reactions, rare metal catalysts, e.g. rhodium or palladium, Raney nickel or cobalt catalysts, in given case on a carrier e.g. on carbon, preferably palladium on activated carbon, more preferably 10% of the compound to be reduced.

The hydrogenation is carried out in an inert organic solvent, preferably in a C_1 - C_4 alcohol, more preferably in methanol, at 10-50°C,

under 1-20 kPa pressure, preferably at room temperature and under atmospheric pressure.

The Michael addition of the ester of cyclohexylidene-acetic acid with nitromethane is carried out in the presence of a base, preferably potassium hydroxide.

The hydrolysis of the alkyl ester group is carried out with base, preferably aqueous methanolic solution of potassium hydroxide at room temperature, then the acid is liberated with 10% aqueous potassium dihydrogenphosphate solution.

After filtration of the catalyst the product is isolated by concentration of the filtrate. The product obtained on concentration is 98-99% pure, the yield is 50-70%.

The advantages of this procedure are as follows:

- the obtained product is very pure
- the number of reaction steps is less than in the known procedures
- the lactam compound, which is very difficult to remove, is not formed
- neither special pressure resistant equipment nor expensive catalyst is needed
- the final product can be obtained without applying difficult and complicated ion-exchange technology
- no poisonous or dangerous materials are needed

Examples

Example 1

a) Synthesis of 1-(nitromethyl)cyclohexyl-acetic acid

A solution of 4.3 g (0.02 mol) of methyl 1-(nitromethyl)cyclohexyl-acetate in a mixture of 50 ml of methanol and 20 ml of 10% aqueous potassium hydroxide is stirred at room temperature for 24 h, then the methanol is distilled off in vacuo. The pH of the resulted aqueous solution is adjusted to 7 with 10% aqueous potassium dihydrogenphosphate solution. The

solution is extracted three times with 30 ml of ethyl acetate, the combined organic layers are dried over sodium sulphate and concentrated to yield 3.2 g (80%) of the title compound as oil.

5 b) Synthesis of 1-(aminomethyl)cyclohexyl-acetic acid

A solution of 2.01 g (0.01 mol) of 1-(nitromethyl)cyclohexyl-acetic acid in 50 ml of methanol is hydrogenated in the presence of 0.2 g of palladium on activated carbon at atmospheric pressure. The catalyst is filtered off and the filtrate is concentrated to 10 ml. 20 ml of tetrahydrofuran is added
10 to the residue and the precipitated crystals were filtered off and dried to yield 1.3 g (80%) of the title compound. Mp: 164-169°C

Example 2

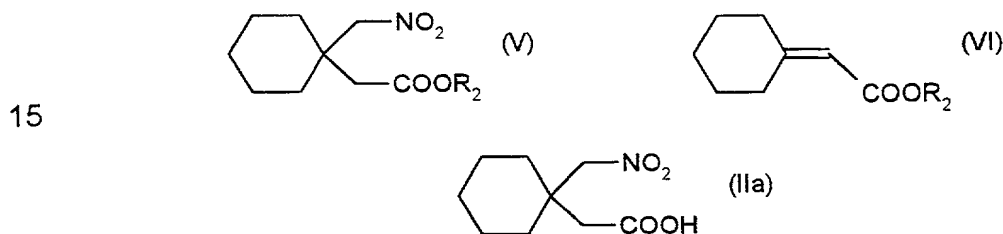
Synthesis of 1-(aminomethyl)cyclohexyl-acetic acid

15 A solution of 5 g (0.017 mol) of benzyl 1-(nitromethyl)cyclohexyl-acetate in 50 ml of methanol is added to a mixture of 0.5 g of prehydrogenated palladium, 10% on activated carbon in 50 ml of methanol. This mixture is hydrogenated at room temperature under atmospheric pressure until the calculated hydrogen is consumed, then the catalyst is filtered off, the
20 filtrate is concentrated to about 15 ml and 30 ml of tetrahydrofuran is added to precipitate the title compound. Yield: 1.5 g (51%). Mp: 168°C.

Claims:

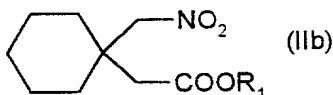
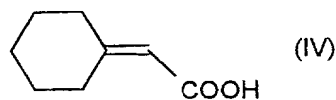
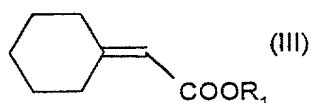
1. Process for the synthesis of 1-(aminomethyl)cyclohexyl-acetic acid and pharmaceutically acceptable salt thereof characterised by

a) transformation of the alkyl ester of cyclohexylidene-acetic acid of formula (VI) — wherein R_2 represents C_1 - C_4 alkyl group — into the alkyl ester of 1-(nitromethyl)cyclohexyl-acetic acid of formula (V) — wherein the meaning of R_2 is as defined above — with nitromethane in the presence of a base, hydrolysis with aqueous methanolic solution of potassium hydroxide and hydrogenation of the obtained 1-(nitromethyl)cyclohexyl-acetic acid of formula (IIa) in the presence of a catalyst and in given case transformation of the obtained compound into a pharmaceutically acceptable salt or



b) hydrolysis of the alkyl ester of cyclohexylidene-acetic acid of formula (VI) — wherein R_2 represents C_1 - C_4 alkyl group — into the cyclohexylidene-acetic acid of formula (IV) with aqueous methanolic solution of potassium hydroxide, reaction of the obtained acid of formula (IV) with a reagent of formula R_1 -X — wherein R_1 represents benzyl group, diphenylmethyl group or in given case C_1 - C_4 alkyl or alkoxy aromatic ring substituted derivatives thereof and X represents halogen atom — to give the intermediar cyclohexylidene acid derivative of formula (III) — wherein the meaning of R_1 is as defined above — transformation of this intermediar into the 1-(nitromethyl)cyclohexyl-acetic acid derivative of formula (IIb) — wherein the meaning of R_1 is as defined above — and

hydrogenation of the latter in a solvent in the presence of a catalyst and in given case transformation of the obtained compound into a pharmaceutically acceptable salt.



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2. Process b) of claim 1 characterised by using benzyl halide as reagent of formula R_1-X .

3. Process b) of claim 1 characterised by using diphenylmethyl halide as reagent of formula R_1-X .

10 4. The process of claim 1-3 characterised by carrying out the hydrogenation in an inert organic solvent.

5. The process of claim 1-3 characterised by using palladium on activated carbon as catalyst.

15 6. The new compounds of formula (II), wherein R represents hydrogen, benzyl, diphenylmethyl group or in given case C_1-C_4 alkyl or alkoxy aromatic ring substituted derivatives thereof.

7. 1-(nitromethyl)cyclohexyl-acetic acid

8. benzyl 1-(nitromethyl)cyclohexyl-acetate

9. diphenylmethyl 1-(nitromethyl)cyclohexyl-acetate

20



21838

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that: My residence, post-office address, and citizenship are as stated below next to my name,
I believe that I am an original joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled

PROCESS FOR THE SYNTHESIS OF 1-(AMINOMETHYL)CYCLOHEXYL-ACETIC ACID

the specification of which was filed on **23 December 1999** as PCT application **PCT/HU99/00102**.
I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under 35 USC 119 of any foreign applications for patent or inventor's certificate listed below and have also identified below any foreign applications for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Applications

Country	Number	Filing Date	Priority claimed
HU	P9803034	29 December 1998	Yes

I hereby claim the benefit under 35 USC 120 of the United States Application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States Application(s) in the manner provided by the first paragraph of 35 USC 112, I acknowledge the duty to disclose material information as defined in 37 CFR 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Serial Number	Filing Date	Status
PCT/HU99/00102	23 December 1999	Pending

I hereby appoint as attorneys to prosecute this application and to transact all business connected therewith: **Herbert Dubno**, Reg. 19,752; **Jonathan Myers**, Reg. 26,963; **Andrew Wilford**, Reg. 26,597 and each of them individually.

Address all correspondence to:

The Firm of Karl F. Ross, P.C.
Customer Number 535

5676 Riverdale Avenue, Box 900
Bronx, New York 10471-0900
(718) 884-6600

Direct all telephone calls to:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or

both, under 18 USC 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first inventor:

1-0

Tibor GIZUR

Inventor's signature

Tibor Gizur

Date: 27.09.2001.

Residence: Budapest, Hungary

Citizen of Hungary

Post-office Address: Avarszallas u. 30, H-1162 Budapest, Hungary

Full name of second inventor:

2-0

Zoltanné LENGYEL

Inventor's signature

Lengyel Zoltanné

Date: 03.05.2001

Residence: Budapest, Hungary

Citizen of Hungary

Post-office Address: Zirzen J. u. 40/c, H-1125 Budapest, Hungary

Full name of third inventor:

3-0

Krisztina SZALAI

Inventor's signature

Szalai Krisztina

Date: 04.05.2001

Residence: Budapest, Hungary

Citizen of Hungary

Post-office Address: Sarkadi ut 2, VI. em. 20, H-1039 Budapest, Hungary